ADHD in Girls: Clinical Comparability of a Research Sample

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ABSTRACT

Objective: The investigation of attention-deficit/hyperactivity disorder (ADHD) in girls raises complex questions of referral bias and selection criteria. The authors sought to determine whether they could recruit a research sample of comparably affected girls using a combination of sex-independent diagnostic criteria and sex-normed cutoffs on teacher ratings. They also report on the largest placebo-controlled crossover comparison of methylphenidate and dextroamphetamine in girls with ADHD. **Method:** Subjects were 42 girls with *DSM-III-R/DSM-IV* ADHD (combined type) contrasted to 56 previously studied boys with ADHD on comorbid diagnoses, behavioral ratings, psychological measures, psychiatric family history, and stimulant drug response. **Results:** Girls with ADHD were statistically indistinguishable from comparison boys on nearly all measures. Girls exhibited robust beneficial effects on both stimulants, with nearly all (95%) responding favorably to one or both drugs in this short-term trial. Dextroamphetamine produced significantly greater weight loss than methylphenidate. **Conclusions:** This highly selected group of ADHD girls was strikingly comparable with comparison boys on a wide range of measures. The results confirm that girls with ADHD do not differ from boys in response to methylphenidate and dextroamphetamine and that both stimulants should be tried when response to the first is not optimal. *J. Am. Acad. Child Adolesc. Psychiatry,* 1999, 38(1):40–47. **Key Words:** attention-deficit/hyperactivity disorder, sex differences, randomized clinical trials, methylphenidate, dextroamphetamine.

The literature on attention-deficit/hyperactivity disorder (ADHD) in girls is scant and inconsistent. Almost all research on ADHD has focused exclusively on boys. This bias reflects male-female ratios in referred samples ranging from 4:1 to 9:1 (American Psychiatric Association, 1994) and the perceived need for homogeneity in research samples. However, community-based studies have found male-female sex ratios as low as 2.1:1 (Szatmari, 1992; Taylor et al., 1998), confirming that girls with ADHD have been neglected by clinicians and researchers (Berry et al., 1985). The discrepancy between clinic and community rates of ADHD in boys and girls and the questions it raises were the focus of a National Institute of Mental Health (NIMH) Conference on Sex Differences in ADHD (Arnold, 1996b). The participants noted the existence of substantial evidence of normative sex differences that influence the manifestations of ADHD, so that the issue of selecting comparable sex-matched subjects for study is not trivial. For example, if identical criteria are used for both boys and girls with ADHD, when the normative populations differ in symptom distribution, then the few girls who meet selection criteria would be expected to exhibit markedly greater severity relative to their same-sex controls. On the other hand, using completely distinct criteria for both sexes, e.g., exceeding the 95th percentile for that sex on all measures, might include girls who are not comparably impaired by their symptoms.

When we embarked on the study of ADHD in girls in 1993, we decided to combine the 2 approaches. That

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is, we required that all subjects meet full criteria for ADHD (initially *DSM-III-R*, later combined type *DSM-IV*). We also required that teachers' hyperactivity ratings exceed the 95th percentile, but set distinct sex-normed cutoffs for boys and girls. We hypothesized that this would allow us to recruit a sample of girls with ADHD of comparable severity to that of previously studied boys. We are now able to examine the results of our recruitment and screening efforts as we prepare data analyses of brain anatomy in girls with ADHD.

There has also been a paucity of randomized, controlled medication trials in girls with ADHD. Two small studies found no differences between boys and girls in response to methylphenidate (Barkley, 1989; Pelham et al., 1989), but there have been no controlled studies of the efficacy of dextroamphetamine in girls. We now report on the largest sample of girls with ADHD to undergo a placebo-controlled crossover comparison of methylphenidate (MPH) and dextroamphetamine (DEX).

METHOD

Subjects

Girls with a history of severe hyperactivity, impulsivity, and inattentiveness that interfered with home and school functioning were recruited for controlled stimulant trials and anatomic brain imaging from local schools and health care providers beginning in 1993. Structured telephone screenings were conducted by research social workers (G.F.R., W.S.S.) to determine that symptoms of ADHD were present in at least 2 settings and that Conners Hyperactivity factor scores from their home teacher were at least 2 SD greater than age and sex norms (≥1.0 for girls versus ≥1.8 for boys, scored from 0 to 3) (Werry et al., 1975). Exclusion criteria were Full Scale IQ less than 80 on the WISC-R (Wechsler, 1974) and chronic medical or neurological diseases, including Tourette's disorder and chronic tic disorders.

From approximately 150 initial inquiries, 65 subjects declined to participate (42 after telephone screening and 23 after submitting initial rating scales) for a variety of reasons including improvement in symptoms, parents' discomfort with medication, or lack of follow-through. We excluded 25 subjects primarily because their hyperactivity symptoms were not sufficiently severe. Other exclusion reasons included the following: IQ < 80 (n = 4), other medical conditions (n = 5), and medications other than stimulants that could not be discontinued (n = 2). Five subjects are not included in the main analyses because they did not also enter the neuroimaging study component. Two other subjects were excluded after completing the study. In one case, we uncovered ongoing sexual abuse that raised questions about the validity of the ADHD diagnosis. In the other, we concluded at the completion of the 3-month day program that impairment was mostly ascribable to severe multiple learning disorders rather than ADHD symptoms. Of the remaining 42 girls, 67% are white, 19% are African-American, and 14% are Latina.

The most common referral sources were local schools (35%) and physicians (24%). Children were also referred by program alumni (10%), the National Institutes of Health (NIH) listing of clinical studies (10%), friends (7%), and the advocacy organization Children and Adults with Attentional Disorders (2%); 2% learned of our study from media reports. Referral sources were unknown for 10%.

Besides the 32 girls who participated in the controlled stimulant trial described below, a second group (n = 10) participated in a pilot study comparing sustained-release DEX, placebo, and the mixed amphetamine compound, Adderall® (unpublished, 1998). Recruitment strategies, the location of the study, the personnel, curriculum, scheduling, and the duration of the studies were identical. The 2 groups of girls did not differ significantly on any measure (data available on request).

Comparison Group

The 56 comparison subjects were all the subjects included in a prior publication (Castellanos et al., 1996b) except for one boy with chronic motor tics. All but one of the boys had also participated in controlled stimulant trials in the same research day program (Castellanos et al., 1996a; Elia et al., 1991). Seventy-three percent of the boys are white, 21% are African-American, 4% are Latino, and 2% are Asian-American.

Measures

Final *DSM-IV* diagnoses were obtained by a child and adolescent psychiatrist combining information from clinical interviews, staff observations, teacher ratings, and parent structured interview with the Diagnostic Interview for Children and Adolescents-Parent Version (Herjanic and Campbell, 1977). Psychiatric diagnoses of day program probands' biological parents were obtained by unblinded in-person interviews using the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott, 1982). We obtained the Wender Utah Rating Scale (WURS) (Ward et al., 1993) from available biological parents to obtain a dimensional measure of childhood ADHD symptoms. Provisional categorical classification of parents into ADHD or non-ADHD groups was performed by using 95th percentile cutoffs for each sex (32 or greater for females, 40 or greater for males) (Ward et al., 1993). Information on ADHD status of siblings was gathered via genograms by requesting that parents categorize the ADHD status of all full siblings aged 7 or older as absent, probable, or definite. Siblings who had been given a medical diagnosis of ADHD and were receiving ongoing stimulant treatment were classified as having definite ADHD.

Psychoeducational evaluation consisted of the WISC-R (Wechsler, 1974) and Woodcock-Johnson Achievement Battery (Woodcock and Johnson, 1977), performed by a psychologist (B.B.K.). Ten of the most recently recruited girls were assessed with the updated versions (WISC-III, Wechsler, 1991; Woodcock-Johnson Revised, Woodcock and Johnson, 1989). Children were classified as having reading disorder if their IQ–Reading discrepancy z score exceeded 1.65 (Frick et al., 1991). We obtained Conners Hyperactivity and Conduct factors (range 0–3), the Child Behavior Checklist (CBCL), and the Teacher's Report Form (TRF) (Achenbach and Edelbrock, 1983) from parents and from the children's home teacher. Overall impairment was quantified using the Children's Global Assessment Scale (C-GAS) (range 0–100) (Shaffer et al., 1983) and the Clinical Global Impressions scale for Severity of Illness (CGI-SI, range 1–7) (Clinical Global Impressions, 1985).

Commission and omission errors on the continuous performance test (CPT) (Rosvold et al., 1956) were obtained during drug-free and/or during placebo phase. Most of the boys had been administered CPT during baseline and drug double-blind periods, thus including placebo. Because of a change in the CPT testing schedule, baseline-only data were available for 21 girls (60%) and placebo-only data for 14 girls (40%). For comparison boys, we randomly selected data from baseline for 32 boys (60%) and for the placebo period for 21 boys (40%) to control for practice effects.

Controlled Trial of Methylphenidate, Dextroamphetamine, and Placebo

Children attended our accredited NIMH school 5 days a week for 3 months with academic instruction in the morning and recreation therapy activities in the afternoon. MPH, DEX, and placebo were packaged in identical capsules by the NIH Pharmacy and administered by NIH nurses in double-blind, randomized order at breakfast and lunch 5 days per week (and by parents on weekends) after a 3-week medication-free baseline. Individual doses were packaged in coded blister packs. Weekend medication compliance was confirmed by weekly telephone contacts. Individual drug dosages were selected for each subject prior to study entry based on body weight and medication history; all subjects underwent stepwise increases in their stimulant dose each week. Each double-blind phase lasted 3 weeks. Conventional doses were used in girls, with daily doses of MPH ranging from 10 mg to 70 mg/day and of DEX from 5 mg to 30 mg/day in 2 divided doses. Mean stimulant doses were 0.45, 0.85, and 1.28 mg/kg per dose for MPH, and 0.23, 0.43, and 0.64 mg/kg per dose for DEX for weeks 1, 2, and 3, respectively. The comparison boys had received a higher range of daily doses (MPH 25–90 mg, DEX 10–45 mg), which had been planned to minimize stimulant nonresponse due to potentially inadequate dosing (Elia et al., 1991).

Weekly outcome measures were parent and NIMH teacher Conners ratings of hyperactivity and conduct, and physician-rated global severity (CGI-SI, C-GAS), global improvement (Clinical Global Impressions-Global Improvement [CGI-GI]) (citations noted above), stimulant-related adverse effects (Guy, 1976), and body weight.

The studies were approved by the NIMH Institutional Review Board, and signed consent and assent were obtained from all parents and children, respectively.

Statistical Analysis

Analyses were performed using SAS for Windows, version 6 (SAS Institute, 1996). One-way ANOVA and *t* tests were used to compare baseline measures including socioeconomic status (Hollingshead, 1975) between the 32 girls in the MPH/DEX trial and the 10 girls who took part in the pilot amphetamine trial. Since they did not differ significantly on any baseline measure, the 2 subsamples were combined and compared with previously studied boys. Repeated-measure ANOVA was used to examine drug and dose effects. Significant ANOVA results were further explored with preplanned Bonferroni *t* tests. For example, significant drug by dose interactions were explored by testing the effects of the highest MPH dose versus the effects of the highest DEX dose. Carryover effects were tested by comparing the teachers' ratings of hyperactivity during the first week across the 6 different randomization schedules using ANOVA for MPH, DEX, and placebo. Drug response was defined as a rating of "very much" or "much improved" on the CGI-GI. Dimensional measures of drug response were calculated as the difference between the average of each subject's 3 weekly teachers' hyperactivity ratings during the placebo phase and ratings for their best week during the medication phases (Rapport et al., 1986). Stepwise multiple regression was used to determine significant moderators of drug response.

Because of extreme outliers, the median test was used to compare girls with boys on CPT commission and omission errors. Chi-square (or Fisher exact test when appropriate) was used to analyze psychiatric diagnoses in subjects and parents of subjects. Parents' psychiatric diagnoses were grouped into affective (major depression, dysthymia, and bipolar disorder), anxiety (panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and phobic disorder), and substance abuse disorders (alcohol abuse and substance abuse). Missing weekly body weight data (9%) were calculated by interpolation. Other missing data (1%) were replaced by cell means. All tests were 2-tailed with $\alpha = .05$.

RESULTS

Table 1 shows characteristics of the study subjects and the male comparison group. Female subjects and their male cohorts did not differ significantly on demographic or psychoeducational measures, with 4 exceptions. Girls had significantly lower Woodcock-Johnson Reading Standard Scores than boys ($p = .04$). Psychoeducational scores were unavailable for 1 boy and for 2 girls who were tested elsewhere too recently to allow valid retesting. Achievement scores of 13 boys who had been given a different test were not included.

Conners teacher, but not parent, ratings of hyperactivity were significantly higher for boys than for girls ($p = .002$), which was not surprising, since the normative sex-appropriate cutoffs we used were higher for boys (1.8 versus 1.0 for girls) (Werry et al., 1975). For the CBCL and TRF factors relating to internalizing (Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, and Thought Problems) and externalizing behaviors (Attention Problems, Delinquent Behaviors, and Aggressive Behaviors), parent data were available for all 42 girls and 43 boys, and teacher data for 40 girls and 38 boys. No significant differences were found for girls with ADHD and comparison boys for either internalizing or externalizing symptoms except that parents rated Attention Problems as significantly more severe for girls ($p = .04$). Globally, girls were rated as significantly more impaired ($p = .0001$) on the categorical CGI-SI, but the sexes did not differ on the continuous C-GAS measure of global functioning.

Comparison boys made more omission and commission errors than girls, although these differences did not reach significance (median test, $p = .19$, $p = .38$, respectively).

Comorbidity

Girls and boys with ADHD were similar in comorbidity, whether defined in general (ADHD plus at least one other diagnosis) (girls 69%, boys 71%) or by indi-

TABLE 1
Means and Standard Deviations of Clinical Characteristics of Girls and Comparison Boys With ADHD

	Girls With ADHD ($n = 42$)	Comparison Boys ($n = 56$)	t	df	p
Age (yr)	8.9 ± 1.7	9.3 ± 1.7	−1.21	96	.23
Age range (yr)	6.2–12.7	6.0–12.5			
Age at onset (yr)	3.6 ± 2.1	2.8 ± 1.9	−1.71	74	.09
SES	48.0 ± 25.8	52.4 ± 26.9	−0.81	94	.42
WISC-R Full Scale IQ	105.2 ± 12.8	109.3 ± 17.7	−1.10	82	.28
WISC-R Verbal IQ	105.6 ± 14.7	109.7 ± 19.8	−0.98	82	.33
WISC-R Performance IQ	104.0 ± 12.9	107.0 ± 15.8	−0.88	82	.38
Woodcock-Johnson Reading Standard Score	95.6 ± 14.3	103.8 ± 16.5	−2.10	67	.04*
Woodcock-Johnson Math Standard Score	96.6 ± 14.5	102.7 ± 19.5	−1.40	67	.17
C-GAS	44.6 ± 4.8	45.3 ± 5.9	−0.66	94	.51
CGI-SI	5.0 ± 0.9	4.4 ± 0.7	4.10	89	.0001*
Teacher Conners					
Hyperactivity factor	2.0 ± 0.6	2.4 ± 0.5	−3.17	90	.002*
Conduct factor	0.9 ± 0.7	1.1 ± 0.5	−1.85	63	.07
Parent Conners					
Hyperactivity factor	2.5 ± 0.5	2.4 ± 0.5	0.96	89	.34
Conduct factor	1.4 ± 0.6	1.4 ± 0.6	−0.18	89	.86
Child Behavior Checklist					
Attention Problems	76.0 ± 7.4	72.4 ± 8.2	2.07	83	.04*
Externalizing Behaviors[a]	70.7 ± 8.8	68.0 ± 9.0	1.39	83	.17
Internalizing Behaviors[b]	63.6 ± 7.8	63.7 ± 9.7	−0.08	83	.94
Total Behavior Problems	71.0 ± 7.0	69.9 ± 7.4	0.70	83	.49
Teacher's Report Form					
Attention Problems	70.3 ± 8.0	70.0 ± 9.5	0.14	76	.89
Externalizing Behaviors[a]	69.7 ± 8.5	68.4 ± 6.6	0.74	76	.46
Internalizing Behaviors[b]	61.0 ± 8.1	63.3 ± 10.1	−1.08	76	.28
Total Behavior Problems	69.3 ± 6.3	70.2 ± 6.9	−0.63	76	.53

Note: SES = socioeconomic status; C-GAS = Children's Global Assessment Scale; CGI-SI = Clinical Global Impressions, Severity of Illness.

[a] Attention Problems, Delinquent Behaviors, Aggressive Behaviors.

[b] Withdrawn, Somatic Complaints, Anxious/Depressed, Social Problems, Thought Problems.

* $p < .05$.

vidual analyses for all diagnoses that were present in either group. Those rates were oppositional defiant disorder (girls 50%, boys 33%, $p = .09$), conduct disorder (girls 2%, boys 7%), major depression (girls 7%, boys 0%, $p = .08$), separation anxiety (girls 2%, boys 0%), specific phobias (girls 7%, boys 0%, $p = .08$), trichotillomania (girls 0%, boys 2%), tic disorders not otherwise specified (girls 2%, boys 13%, $p = .13$), enuresis (girls 12%, boys 18%), and reading disorder (girls 8%, boys 5%).

Parents' Diagnoses

There were no significant differences between parents of day program girls and parents of comparison boys on affective disorders (30% and 39%, respectively), anxiety disorders (25% and 14%, respectively, $p = .08$), or substance abuse disorders (19% and 16%, respectively). Twenty parents of girls (24%) and 30 parents of boys (24%) did not meet criteria for any psychiatric diagnosis.

Parental self-report of childhood ADHD symptoms, as quantified by WURS scores, did not differ significantly in dimensional analysis. Group means were 25.0 ± 18.1 and 33.7 ± 17.6 for fathers and mothers of girls, respectively; and 29.0 ± 15.1 and 26.1 ± 20.4 for fathers and mothers of boys, respectively. When we used categorical cutoffs (≥40 for fathers and ≥32 for mothers), a larger proportion of the parents of girls than of boys had scores in the ADHD clinical range (47% versus 24%, $p = .007$). This difference was found only in mothers of girls compared with mothers of boys (62% versus 31%, $p = .008$); the difference between fathers of girls and fathers of boys was not significant (30% versus 21%, respectively).

ADHD in Siblings

A significantly higher proportion of full siblings (aged 7 or older) of girls with ADHD were categorized as having definite or probable ADHD compared with siblings of comparison boys (50% versus 16%, $p = .004$), regardless of whether the sibling was male or female.

Controlled Comparison of Methylphenidate, Dextroamphetamine, and Placebo

All subjects completed the trial with the exception of one 6-year-old for whom the placebo phase was blindly truncated to 2 weeks because of her severe physical impulsivity, without informing staff, parents, or the child. In this case, last observations were carried forward.

Remarkably, none of the 180 possible pairwise comparisons (4 measures $\times$ 3 drug phases $\times$ 15 pairs) yielded significantly different results on carryover analysis. Individual weekly ratings demonstrated highly significant main effects of drug ($F > 58.22$, $p < .0001$) and of dose ($F > 15.06$, $p < .0001$) on all measures demonstrating robust dose-related stimulant effects relative to placebo. Absence of "dose-related" change on placebo was highlighted by more moderate, although still significant, drug by dose interactions for all 4 weekly measures: CGI-SI ($F = 2.56$, $p = .04$), C-GAS ($F = 6.76$, $p = .0001$), and Conners teacher and parent Hyperactivity factor ($F = 9.21$, $p = .0001$; $F = 4.08$, $p = .004$, respectively).

Global improvement (CGI-GI) is illustrated in Figure 1. Five girls (16%) were judged to have improved substantially on placebo. Twenty-two girls (69%) improved substantially on both MPH and DEX. Nine of the remaining 10 responded to one stimulant but not the other (4 to MPH, 5 to DEX). Thus the response rate to either MPH or DEX for study completers was 97%. We found the same high total rate of response (37/39 = 95%) when we included all initially enrolled subjects. For the comparison boys, 69% responded to MPH and 72% to DEX, with a response rate of 87% to one or the other stimulant.

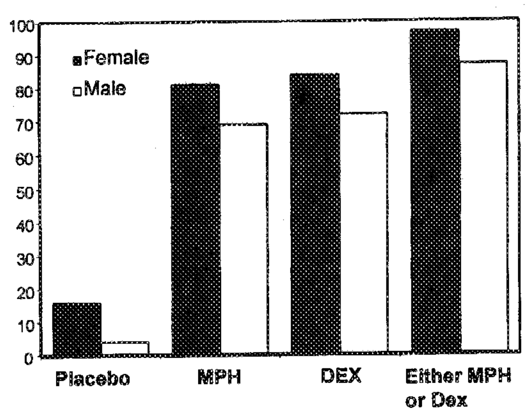

Fig. 1 Percentages of 32 girls and 45 boys with attention-deficit/hyperactivity disorder who had double-blind Clinical Global Impressions-Global Improvement ratings of "very much improved" or "much improved." MPH = methylphenidate; DEX = dextroamphetamine.

Mean beneficial and adverse effects of DEX and MPH were nearly identical for all ratings, including ratings of appetite problems. However, objectively verified significant decreases in body weight (drug main effect, $F = 10.27$, $p = .0002$) were significantly greater for DEX (mean change -1.1 ± 1.0 kg from baseline, $p = .01$) than for MPH (-0.4 ± 1.1 kg, not significant).

The only significant predictor of improvement on teacher ratings of hyperactivity was baseline severity ($R^2 = 0.54$, $p < .0001$). Thirty-one of the 32 female subjects were prescribed a stimulant at discharge: 47% received MPH (29.0 mg/day $\pm$ 15.1) and 50% received DEX (18.1 mg/day $\pm$ 6.2). Stimulant medications were not recommended at discharge for one subject because neither medication substantially improved her ADHD behaviors beyond placebo. One child who was classified as a nonresponder on all 3 phases while in the day program exhibited moderately improved behaviors on DEX at home and was discharged on DEX 7.5 mg b.i.d. Of the comparison boys, 51% had been discharged on MPH (46.1 mg/day $\pm$ 20.9), 45% on DEX (27.1 mg/day $\pm$ 8.9), and 2 children with the recommendation of either stimulant. Ten boys were in a pemoline/placebo study, and their results are not included.

DISCUSSION

In this referred and highly selected sample (<30% of initial inquiries), girls with *DSM-IV* combined type ADHD were strikingly similar to the boys with ADHD we previously studied. On the other hand, with the exception of the Conners teachers' ratings of hyperactivity, when there were significant differences, they were in the direction of greater severity for girls than for boys. Thus, girls had significantly lower reading scores than did boys, though the prevalence of reading disorder was low in both groups. Of the CBCL factors, the Attention Problems score is the best positive predictor of ADHD diagnosis (Hudziak, 1997). Parent-rated Attention Problems *T* scores were significantly higher in the girls than in the boys, but this difference was not supported by the comparable teacher ratings. On physician-rated global impairment, girls had higher severity than boys on one scale (CGI-SI) but not on another (C-GAS). Diagnostically, there were no significant differences in comorbidity patterns in probands or in their biological parents, although there were statistical trends toward a higher prevalence of oppositional defiant disorder, major depression, and specific phobia in girls. The overall pattern of comparable impairment in referred girls with ADHD is consistent with a recent meta-analysis (Gaub and Carlson, 1997). The tendency toward somewhat greater severity on some measures also echoes recent findings in an epidemiologically ascertained sample (Heptinstall et al., 1998).

Also in support of the hypothesis that girls who are referred represent a more extreme sample than clinic-referred boys was our finding of greater familiality of ADHD for parents (at least for mothers) and siblings of girls with ADHD in comparison with relatives of boys. The largest community-based twin study found that females with ADHD have a higher frequency of first-degree relatives with ADHD than do ADHD males (Rhee et al., in press). Their analyses were consistent with a multiple threshold model for the sex differences in ADHD, with diagnosed females having a higher threshold. In clinic-referred samples, results differ. Two studies found no significant difference in familiality based on sex (Faraone et al., 1991; Mannuzza and Gittelman, 1984), but another study reported greater familiality in families of female probands (only in families with antisocial disorders) (Faraone et al., 1995).

Confirmation of greater familiality in families of female probands would have substantial implications for genetic studies. However, we view our results with caution for 3 reasons. First, we did not obtain the samples contemporaneously; thus we did not control cohort effects, such as the dramatic increase in the rate of diagnosis and stimulant treatment of ADHD in the 1990s (Safer et al., 1996). Second, parental ADHD status was determined from a single self-report checklist (WURS) rather than from structured retrospective interviews, and we did not obtain collateral documentation (such as old report cards or grandparent reports). Finally, we did not obtain blinded structured psychiatric interviews for siblings, but rather used a brief genogram interview and/or family medical history to ascertain presence or absence of ADHD.

Thus, our primary conclusion is that our sample of girls demonstrated very similar patterns of comorbidity and impairment and identical patterns of drug response. Their neurobiological data should be informative when compared with and contrasted to that of our previously studied boys, particularly because brain structures of interest in ADHD, such as the caudate nucleus (Swanson et al., 1998), are sexually dimorphic in healthy children, with proportionately larger volumes in girls (Giedd et al., 1997).

Clinical Implications: Sex Differences in ADHD

There is a popular notion that girls with ADHD have primarily attentional difficulties and a later age at onset than boys. In our samples, age at onset did not differ significantly. We also found a higher frequency of oppositional defiant disorder in our sample of girls, possibly because of selection and referral bias. The following vignettes provide a qualitative "flavor" of a representative selection of our subjects.

Case 1. A was a 6-year-old who began to take MPH at age 2½ years, when ADHD was diagnosed. Her family history is negative for ADHD. She was asked to leave a prekindergarten program because of her "disruptive behavior." Although academically on grade level, she jumped from task to task, had difficulty focusing, marked furniture with crayons, and crawled and hid under her desk. At home, she was in constant motion; she ran into the street several times without checking for cars, narrowly avoiding serious accidents. During the study, A almost lost transportation privileges because she did not stay seated on the van. Her placebo phase was shortened because of severe impulsivity that endangered her safety. At the time of discharge, A was receiving 10 mg of DEX twice a day.

Case 2. B was a 7-year-old who began to take MPH at age 6 years, when ADHD was diagnosed. Her brother and mother also had ADHD. B's teacher noted that she reacted quickly and impulsively, without thinking about consequences, and that peers did not want to sit near her because she hit or kicked them. Her parents complained that B sat only briefly and often ate dinner swinging her legs or sitting on her knees. B ran away from her parents or hit them when frustrated. During the study, B was usually able to stay in her chair but the chair and desk would gradually move across the classroom as a result of her constant fidgeting. B also had oppositional defiant disorder; at discharge she was prescribed 5 mg of MPH each morning and 2.5 mg at lunch.

Case 3. C was an 11-year-old whose ADHD was diagnosed at age 6 years. A brief trial of MPH was discontinued because of maternal concern. C's father may have had ADHD as a child; otherwise, the family history was reported as negative. Her mother described C as stubborn, impatient, and intrusive. Her performance was below grade level in math and reading, and she could not stay in her seat at school. C was suspended twice for physical aggression. During the study, C threatened students and once shoved a classmate. C denied responsibility when confronted, and she appeared unaware of others' "personal space." C's artwork often displayed poor self-control; she once covered her paper with a thick layer of black chalk and then proceeded to smear black chalk on the bathroom walls. C also had oppositional defiant disorder; at discharge she was prescribed a 15-mg DEX Spansule® each morning and a 5-mg DEX tablet after school.

Clinical Implications: Controlled Trial of Methylphenidate and Dextroamphetamine

Previous smaller studies of girls with ADHD have found that the response to MPH is comparable in both sexes (Barkley, 1989; Pelham et al., 1989). In this, the largest controlled stimulant trial in girls with ADHD, we replicated the prior observation in boys that MPH and DEX are comparably effective and that the rate of efficacy is even higher when both drugs are considered (Elia et al., 1991). Our findings were strikingly robust, especially considering that we used lower doses and a more conservative definition of drug response than had Elia et al. (1991). It thus supports the recommendation that whenever the response to the first stimulant tested is suboptimal, the alternative stimulant should be tried (Arnold, 1996a). However, our results are derived from a short-term trial in a structured research day program in highly selected subjects, and thus they may not apply to samples with more comorbid disorders (Tannock et al., 1995) or less distinct cases of combined type ADHD (Spencer et al., 1996).

Regarding choice of first stimulant, MPH and DEX were indistinguishable on all measures of efficacy and adverse effects with one exception. DEX produced a significant mean loss in body weight, whereas MPH did not. Our data thus provide additional support (see also Efron et al., 1997a,b) for the usual clinical practice of beginning most stimulant trials with MPH.

Other Limitations

As noted above, the present sample and the comparison boys were not studied contemporaneously. Nevertheless, the continuity of program, staff, referral sources, and diagnostic instruments appears to have mitigated this potential confound. We also combined subjects from 2 separate clinical trials, but we found that the 2 subsamples were statistically indistinguishable, and our conclusions would have been unchanged if we had reduced the sample of girls to 32. Finally, in the interest of continuity, we used older versions of psychoeducational instruments, thus necessitating caution in comparing our specific numerical values to other samples.

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